Supplementary file

METHODS

Differential scanning calorimetry (DSC) studies

For DSC studies, TT, Eudragit E 100, Eudragit RSPO, Eudragit RLPO 100, and PVP were evaluated for their xcipient-drug compatibility. DSC was used to characterize the thermal behaviour and to confirm the compatibility of each ingredient with TT in the mixture. Approximately 10–20 mg of physical mixture samples was weighed into an aluminum crucible and placed in the instrument. The samples were scanned in DSC 823^e (Mettler Toledo, USA) and heated to the temperature range 0–260 °C at a rate of 10 °C min^{-1} (Fig. 1).

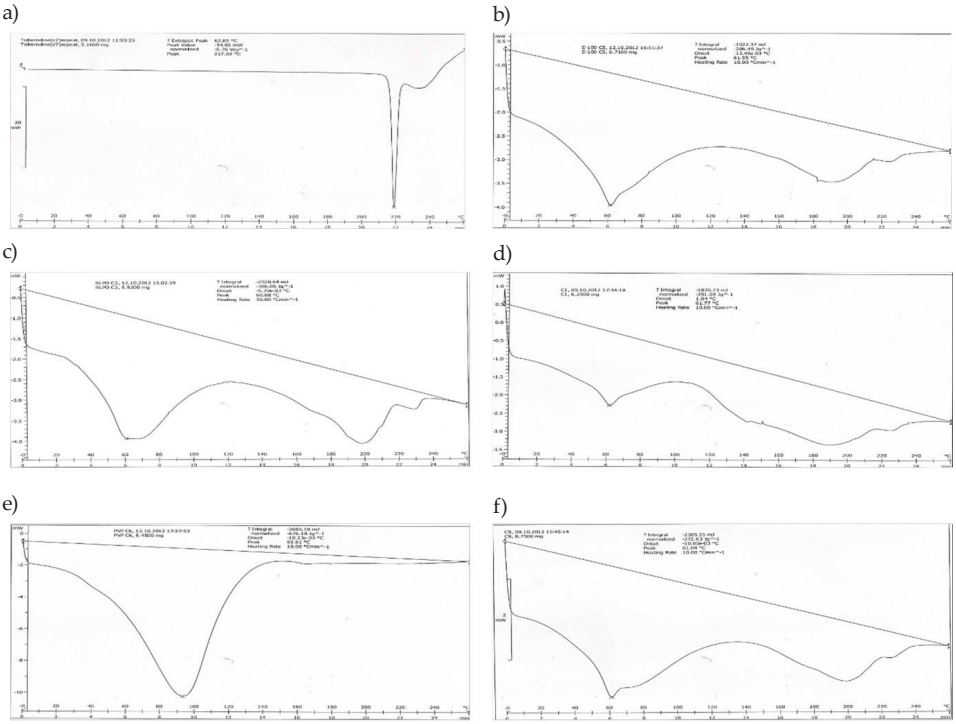
Skin irritancy test

Localized skin reactions were determined using a skin irritation test on male albino rats weighing between 150 and 180 g with slight modifications to the mentioned method (1). Five groups of animals were used to evaluate skin irritation: the first group received doubly distilled water, the second group received a control matrix patch without TT, the third group was the irritant, 0.8 % (*V*/*V*) aqueous formalin solution, the fourth group was administered the C1 patch, while the fifth group received the E1 patch. Optimized patches (2 cm^2) or one mL of formalin solution were administered once for three consecutive days onto a 2 cm^2 shaved area on the dorsal side. Table I presents the intensity of the observed localized reactions of the animals.

RESULTS AND DISCUSSION

Differential scanning calorimetry studies

The copolymer PVP peak is shown at 92.81 °C in Fig. 1e. For further confirmation of the compatibility of polymers, copolymers and the drug were studied extensively by DSC. The DSC thermogram of TT was typical of a crystalline substance, exhibiting a sharp exothermic peak at 217.02 °C (Fig. 1a), which corresponds to the melting point of the drug. Three different Eudragit grades, E 100, RLPO and RSPO, are shown in Figs. 1b, 1c and 1d. These Eudragits grades showed an endothermic peak at 61 °C and the same endothermic peak was observed in the transdermal patch at 61 °C (Fig. 1f). All three Eudragit polymer peaks showed an endothermic peak at the same temperature (61 °C) and the same endothermic peak was observed in the transdermal patch, which indicated that there was no incompatibility between the drug and the polymers. The endothermic peak of the TT transdermal patch appeared (at around 205 °C) due to the loss of sorbed water in the presence of PVP in the matrix film. The polymer PVP thermogram peak is not evident in the patch and this indicates that the PVP may be dispersed in Eudragit polymeric chain spac-



Supplementary Fig. 1. DSC Spectra of: a) tolterodine tartrate, b) Eudragit E-100, c) RLPO, d) RSPO, e) PVP, f) transdermal patch.

es at the molecular level. It is clear from the results that addition of Eudragit into the transdermal patch may prevent crystallization of TT; it may also be possible that plasticizer effectively increases the space between the polymer chains and helps the dispersion of PVP and TT, thus leading to the disappearance of the peak.

Skin irritation test

Transdermal patches were evaluated for skin irritation (C1 and E1). Skin safety results are given in Table I. The data was interpreted as per the classical Lehman's skin irritation test, which ascertained that these matrix patches with smaller than 2 primary irritation index (PII) were non-irritants (2).

It is of the paramount importance to have non-irritable components in the matrix patch for transdermal delivery, since they remain in the skin longer than conventional gels. The results indicate that the matrix patch intended for transdermal delivery is a good skin compatible controlled drug release formulation. The different Eudragit grades, which are pH sensitive polymers, may be inert on the skin.

Supplementary Table I. Skin irritation test

Rats	Control		Control patch		Formalin Solution		C 1		E 1	
	Ery-thema	Edema	Ery-thema	Edema	Ery-thema	Edema	Ery-thema	Edema	Ery-thema	Edema
1	0.0	0.0	0.0	0.0	4	1	0.0	0.0	1	0.0
2	0.0	0.0	0.5	0.0	3	2	0.5	0.0	0.5	0.0
3	0.0	0.0	0.5	0.0	3	3	1	0.0	0.5	0.0
4	0.0	0.0	0.5	0.0	4	2.5	0.5	0.0	0.5	0.0
5	0.0	0.0	0.0	0.0	4	3	1	0.0	1	0.0
6	0.0	0.0	0.5	0.0	3	2.3	0.5	0.0	0.5	0.0
Mean	0.0	0.0	0.0	0.0	3.5	2.5	0.58	0.0	0.66	0.0
SD	0.0	0.0	0.2	0.0	0.64	0.28	0.19	0.0	0.17	0.0
PII	0.0 ± 0.0		0.33 ± 0.05		5.03 ± 0.74		0.42 ± 0.09		0.26 ± 0.07	

PII – Primary Irritation Index (n = 6); Visual observation values are expressed as mean ± SD, n = 6. Control – untreated rats; control patch – transdermal patch without drug; negative control – formalin solution; C1 – transdermal patch; E1 – transdermal patch. Erythema scale: 0 – none, 1 – slight, 2 – well defined, 3 – moderate, 4 – scar formation. Edema scale: 0 – none, 1 – slight, 2 – well defined, 3 – moderate, 4 – severe.

REFERENCES

1. R. Rajabalaya, S. R. David, J. Chellian, G. Xin Yun and S. Chakravarthi, Transdermal delivery of oxybutynin chloride proniosomal gels for the treatment of overactive bladder, *Drug Deliv.* **23** (2016) 1578–1587; DOI: 10.3109/10717544.2015.1116027.
2. B. Nasseri, Effect of cholesterol and temperature on the elastic properties of niosomal membranes, *Int. J. Pharm.* **300** (2005) 95–101; DOI:10.1016/j.ijpharm.2005.05.009.